WRITTEN REPLY

To: Munehiko Higuchi, Examiner of Patent Office

1. Representation of International Application

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4. Date of Notification

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5. Content of Reply

We have made an amendment, as in the attached amendment, to the points suggested by the examiner in the second written opinion of International

Preliminary Examining Authority. We hereby reply on the line of the amendment.

(Regarding the subject invention)

The invention in claim 1 of the subject invention includes the constituent features of "comprising a sensor unit having a metal layer with a plurality of convex parts or concave parts formed by fixing metal particles having a diameter of between 10 and 30 nm at an interval of greater than or equal to two times and less than or equal to four times the diameter in average from each other on a surface of a transparent substrate, and molecule recognition functional substance for attaching a specific analyte immobilized on the substrate or the metal layer; wherein the surface arranged with the metal layer and the molecule recognition functional substances of the sensor unit is contacted to an analysis sample solution containing analyte modified with a light emitting molecule; an evanescent light generated at the surface of the substrate by an excitation light irradiated at an incident angle totally reflected at the surface of the substrate onto the other surface of the sensor unit and the metal layer plasmon resonate to locally intensify an electric field around the metal layer; and presence or concentration of the analyte attached to the molecule recognition functional substance is measured by detecting a luminescent light excited and emitted from the light emitting molecule of the analyte attached to the molecule recognition functional substance among the anlaytes with the electric field".

In particular, by including the constituent feature of "a metal layer with a plurality of convex parts or concave parts formed by fixing metal particles having a diameter of between 10 and 30nm at an interval of greater than or equal to two

times and less than or equal to four times the diameter in average from each other on a surface of a transparent substrate", the electric field can be enclosed in the vicinity of the metal fine particles, and thus only the light emitting molecule modifying the analyte attached to the molecule recognition functional substance emits light. Therefore, the production of noised by the light emission of the light emitting molecule modifying the anlayte not attached to the molecule recognition functional substance is prevented, thereby allowing the presence or the amount of the specific analyte attached to the molecule recognition functional substance to be measured at satisfactory precision.

The invention described in claim 1 also includes the constituent feature of "an evanescent light generated at the surface of the substrate by an excitation light irradiated at an incident angle totally reflected at the surface of the substrate onto the other surface of the sensor unit and the metal layer plasmon resonate". According to such constituent feature, the excitation light from the transparent substrate towards the metal fine particles side excites the metal fine particles and the excitation light returning from the metal fine particles side towards the transparent substrate excites the metal fine particles through the use of the Goos-Hanchen effect, thereby enhancing the bonding efficiency between the metal fine particles and the excitation light.

Therefore, the light emitting molecules more strongly emit light since a stronger electric field is generated in the vicinity of the metal fine particles, wherefore a localized plasmon resonance sensor having satisfactory S/N ratio of the signal and high detection accuracy is realized.

Similar to claim 1, the invention of claim 21 of the present invention includes the feature of "having a metal layer with a plurality of convex parts or

concave parts formed by fixing metal particles having a diameter of between 10 and 30nm at an interval of greater than or equal to two times and less than or equal to four times the diameter in average from each other on a surface of a transparent substrate", and a feature of "generating an evanescent light at the surface of the substrate by irradiating an excitation light at an incident angle totally reflected at the surface of the substrate to a surface not arranged with the metal layer and the molecule recognition functional substances of the sensor unit". Therefore, similar to the explanation for the invention of claim 1 of the subject invention, the bonding efficiency between the metal fine particles and the excitation light is enhanced through the use of the Goos-Hanchen effect and a stronger electric field is generated in the vicinity of the metal fine particles, wherefore a measurement method having satisfactory S/N ratio of the signal and high detection accuracy is realized.

(Comparison with cited documents)

In cited document 1, the invention of a method and a device of generating local plasmon by using a sensor film distributed with metal fine particles and irradiating the excitation light thereon, and performing spectral measurement of the Raman scattering when the local plasmon resonate with the vibration mode of the molecular bond is described. The preferred diameter of the metal fine particles is described as between 0.3 and 20 nm, and the average distance between the fine particles is described as preferably between 1 and 10 nm.

Cited document 2 describes arranging concave parts periodically in the metal thin film in terms of strengthening fixation in the fluorescence measurement device using the evanescent light.

Cited document 3 also describes arranging concave parts periodically in the metal thin film in the fluorescence measurement device using the evanescent light.

Cited document 4 describes exposing the molecule recognition functional substance immobilizing surface to the inside of the flow cell flow path in surface plasmon analysis.

Cited document 5 describes having one part as dielectric and one part as metal in the metal fine particles used in analysis with the evanescent light to immobilize the molecule recognition functional substance such as antibody only at the metal portion.

Cited document 6 describes arranging the prism for excitation light entrance closely attached to the back surface of the sensor substrate, arranging a light collecting lens at the pre-stage of the fluorescence detector, and arranging an excitation light cut filter in the fluorescence measurement light path in the fluorescence analysis using the evanescent light.

Cited document 7 describes arranging a plurality of metal thin film portions on the substrate and immobilizing different molecule recognition functional substances for each portion to simultaneously measure a plurality of types of molecules in the surface plasmon analysis.

Cited document 8 describes an analysis technique of performing fluorescent excitation under the coexistence of the surface plasmon wave and the evanescent light.

However, no teachings nor suggestions on the features of "a metal layer with a plurality of convex parts or concave parts formed by fixing metal particles having a diameter of between 10 and 30 nm at an interval of greater than or

equal to two times and less than or equal to four times the diameter in average from each other on a surface of a transparent substrate", and "an evanescent light generated at the surface of the substrate by an excitation light irradiated at an incident angle totally reflected at the surface of the substrate onto the other surface of the sensor unit and the metal layer plasmon resonate" described in claim 1 of the subject invention are found in any of the documents of cited documents 1 to 8. The invention described in claim 1 of the subject invention cannot be easily contrived even if the cited documents 1 to 8 are combined, and the localized plasmon resonance sensor having high detection accuracy cannot be provided as in the subject invention.

Therefore, the invention described in claim 1 and the dependent claims thereof (claims 3 to 6, 12, 13, 15 to 20) of the subject invention are considered to have an inventive step. Similarly, the invention described in claim 21 cannot be easily contrived by combining the cited documents. Therefore, the invention described in claim 21 and the dependent claim thereof (claim 22) is considered to have an inventive step.